D. Remarks:

Upon entry of the present amendments, claims 1-3, 6, and 13-14 are pending in the application. Claim 1 has been amended to more particularly define the subject matter of the invention. Support for the amendment can be found at least in the claims as filed or as previously presented, and at page 39, lines 3-8 and at page 41, lines 11-17 of the specification as filed. Claim 4 has been canceled herein. No new matter has been added.

Applicant acknowledges with appreciation that the rejection of claim 2, under 35 U.S.C. § 112, ¶ 2, has been withdrawn.

Priority

The Examiner had indicated that the priority claim does not meet the formal requirements of 35 U.S.C. § 120. According to the Examiner, none of the prior applications from which the instant application claims priority share a common inventor with the inventor named in the instant application. Therefore, the Examiner notes that the effective filing date of the instant application is October 20, 2000, its filing date. Applicant disagrees.

Applicant has herein amended the specification to delete priority claims to prior applications 09/339,093, 08/926,313, 09/486,302, and PCT/US98/18597. Accordingly, the sole remaining application to which the instant application claims priority is USSN 60/160,553 ("the '553 application"), filed on October 20, 1999.

Moreover, Applicant submits herewith a copy of a Request for Correction of Inventorship under 37 C.F.R. §§ 1.48(d) and 1.48(e) for the '553 application, filed concurrently with the Petitions Office on this day. As indicated in the Request, the sole inventor of the instant application, Anders Björklund, was erroneously omitted as an inventor of the '553 application. Björklund was inadvertently not named as an inventor through no deceptive intent on his part. Likewise, as also indicated in this Request, Rosemary Fricker (now Rosemary Fricker-Gates) was erroneously named as the sole inventor of the '553 application. This error was inadvertent and occurred through no deceptive intent on her part.

Thus, as indicated in the attached Request, Anders Björklund is the sole inventor of the '553 application. Therefore, upon correction of the inventorship of the '553 application, Applicant submits that the instant application and the '553 application will share a common

inventor (Anders Björklund). Accordingly, Applicant submits that the instant application is entitled to the benefit of the October 20, 1999 effective filing date.

Specification.

The Examiner objects to the disclosure for containing an improper priority claim. As discussed above, Applicant has amended the specification to delete priority claims to applications 09/339,093, 08/926,313, 09/486,302, and PCT/US98/18597. A Supplemental Declaration and Power of Attorney to correct the priority claim is not believed necessary in view of MPEP § 201.11, III, G. However, Applicant can submit one upon the Examiner's request.

Accordingly, the objection should be withdrawn.

Rejection under 35 U.S.C. § 112, ¶ 1.

The Examiner maintains the rejection of claims 1-4, 6 and 13-14 for lack of enablement. Specifically, the Examiner contends that the specification is insufficient to meet the "how to use" requirement of 35 U.S.C. § 112, first paragraph. *See* Office Action, p. 3. The Examiner asserts that there is a sole utility asserted for the claimed invention; namely, the production of a therapeutic effect or benefit in an animal. According to the Examiner, the specification does not teach how to use the methods of the invention to produce such a therapeutic benefit or effect. *See* Office Action, p. 3. Claim 4 has been cancelled. Thus, this rejection is moot as it applies to this claim. Moreover, applicant disagrees as this rejection is applied to claims 1-3, 6 and 13-14, as amended.

1. The Standard for Enablement

Under 35 U.S.C. § 112, first paragraph, lack of enablement is found only if one reasonably skilled in the art could not make or use the invention from the disclosures in the patent coupled with information known in the art, without undue experimentation. *See* United States v. Telectronics, Inc., 857 F.2d 778, 785 (Fed. Cir. 1988); In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988); and M.P.E.P. § 2164.01(c). Even if the experimentation required is complex, it is not necessarily undue if artisans skilled in the relevant art typically engage in such experimentation. *See* In re Certain Limited-Charge Cell Culture Microcarriers, 221 U.S.P.Q.

1165, 1174 (Int'l Trade Comm. 1983); and Telectronics, Inc., 857 F.2d 778 (Fed. Cir. 1988) (holding that $50,000 and 6-12 months of experimentation failed to show undue experimentation because the specification contained a working example within the scope of the claims).

The factors used to determine whether experimentation is undue include, but are not limited to the following: (1) the breadth of the claims; (2) the nature of the invention; (3) the amount of direction provided by the inventor; (4) the existence of working examples; (5) the level of predictability in the art; (6) the state of the prior art; (7) the level of one of ordinary skill in the art; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *See* In re Wands, 858 F.2d at 737. No one of these factors is dispositive and the Examiner must consider the evidence as a whole. *Id.*; M.P.E.P. § 2164.05.

Specifically, the "how to use" requirement of § 112, first paragraph, is satisfied if "the specification contains within it a connotation of how to use and/or the art recognizes that standard modes of administration are known and contemplated." *See* M.P.E.P. § 2164.01(c), emphasis added). That section of the MPEP states that "it is not necessary to specify dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph."

The specification here contains much more than the required "connotation" of how to use the claimed invention. Further, the specification and evidence of record demonstrate that the ordinarily skilled artisan could discern an appropriate method of use without undue experimentation.

Here, one of ordinary skill in the art would be able to routinely use the methods described in the application to induce migration of transplanted neural stem cells via infusion of a mitogenic growth factor. For example, claim 1 as amended herein is directed to a method to transplant at least about 500,000 transplanted neural stem cells that are capable of differentiating into neurons, oligodendrocytes, or astrocytes. In this method, at least 500,000 neural stem cells are transplanted to a first locus of the brain of a living host. Following infusion of a mitogenic growth factor at a second locus of the brain, the undifferentiated neural stem cells migrate *in vivo*

from the first locus toward the second locus of the host's brain. The cells maintain the ability to differentiate *in situ* into neurons, oligodendrocytes, or astrocytes. Support for this method is found throughout the specification, and particularly within Example 15 (*See, e.g.*, Specification, page 31, line 23 through page 32, line 3; page 35, line 24 through page 36 line 2; page 37, lines 1-9; and page 41, lines 11-12.)

Furthermore, as indicated by the specification, *in vivo* regulation of neural stem cells transplanted into the brain guides cell migration and/or differentiation, increases graft survival and promotes reinnervation of host tissue, and promotes associated behavioral recovery, enhances the effectiveness of neural stem cell transplantation to serve as a restorative therapy for treating neurodegenerative diseases (*see* Specification, page 41, lines 12-17). Applicant asserts that such a result is indicative of a therapeutic benefit or effect of the claimed invention.

Claim 1, as amended herein, does not require that a specific "therapeutic benefit/effect" be achieved. Rather, claim 1 recites methods for transplanting neural stem cells into a first locus of the brain by infusing a mitogenic growth factor at a second locus, thereby causing the cells to migrate toward the second locus. As demonstrated below, the specification and Examples, taken as a whole, teach those of ordinary skill in the art how to use the claimed methods.

2. The Teachings of the Specification

The specification considered as a whole sets forth how to use the claimed invention in a manner commensurate in scope with the protection sought by the claims. There is ample intrinsic evidence of record that demonstrates how to transplant specific cells (*e.g.*, neural stem cells, as recited in the claims) into the brain of a living host subject and that are known to have the ability to migrate and differentiate, thereby increasing graft survival and enhancing the effectiveness of the transplantation (*See, e.g.*, Specification, page 6, line 24 through page 7, line 7; and Examples 9 and 15).

The instant specification teaches transplanting 250,000 – 500,000 neural stem cells to the brain of a subject under anesthesia by stereotaxic surgery (*See* Specification at page 14, line 23 through page 16, line 16; page 25, lines 20-23). In addition, the specification teaches that the cells can be injected into multiple sites of the brain, including the striatum of the brain, parenchymal sites of the CNS, and intrathecal sites of the CNS (*See* Specification at page 14, line

23 through page 16, line 16; page 25, lines 20-23). The cells can be derived from any suitable tissue source, such as mammalian embryonic tissue (*see* page 15, line 5) and can be cultured in a suspension culture or an adherent culture prior to transplantation (*See* Specification, page 7, lines 5-7; and page 15, lines 4-6). Furthermore, the specification teaches the placement of an infusion cannulae by which to deliver the growth factor within the host in the lateral ventricle (*See* Specification at page 14, line 24-26).

The specification also provides guidance as to the amount of growth factor to be infused. For example, the specification teaches that the total dose required to induce migration and proliferation of transplanted cells will vary from subject to subject, but may be, for example, about 400 ng/day of EGF infused (*See* Specification at page 15, line 22).

Finally, the specification teaches that the infused growth factor regulates the implanted neural stem cells by inducing their migration toward the source of the infused growth factor and that the newly generated cells mass subsequently differentiate into neurons, astrocytes, and oligodendrocytes (*See* Specification, page 15, line 26 through page 16, line 16).

3. Working Examples

The claims as amended herein recite methods for transplanting undifferentiated neural stem cells capable of differentiating into neuron, oligodendrocytes, or astrocytes to a first locus of the brain. Following infusion of a mitogenic growth factor at a second locus of the brain, the cells are induced to proliferate and migrate to the second locus, and then differentiate. There are multiple references to this in the specification and in the working examples, (*see, e.g.*, pages 14-16, 18-20, 25-26, and Examples 8, 9, 10, and 15).

In particular, Applicant has provided several working examples, including Examples 8, 9, and 15, which, taken together, illustrate the methods of the claimed invention. The specification describes the procedures for transplanting neural stem cells (*See* Examples 8, 9, and 15). Moreover, several of the working examples demonstrate the responsiveness of the transplanted cells to an EGF infusion (*See* Examples 9 and 15). In fact, the Examples note that "[m]inimal migration was demonstrated in the adult CNS in the absence of EGF." (*See* Specification, page 26, lines 13-15; *see also* page 33, line 19 through page 34, line 21 and page 35, lines 19 through page 37, line 9). Likewise, the results presented in Example 15 "indicate that neural growth

factor infusion can stimulate murine progenitor cells *in vivo*, after transplantation into the adult rat brain" (*See* Specification, page 41, lines 11-12).

For instance, Example 15 describes the induction of *in vivo* proliferation and migration of transplanted progenitor cells in the brain. As described in Example 15, approximately 500,000 neural stem cells were transplanted into Sprague-Dawley rats. (*See* Specification, page 31, lines 23-25). "Immediately after transplantation, a steel infusion cannula was placed in position in the ventricle . . . Infusion was over 7 days with either 400 ng/day EGF dissolved in a solution of 0.1% rat serum and 0.01% gentamycine in 0.9% saline or control vehicle without EGF." (*See* Specification, page 31, line 26 through page 32, line 3). Following EGF-infusion, "there was a striking pattern of M2-positive staining outside the graft core only on the side toward the lateral ventricle . . . There was a significant increase in the number of profiles stained with M2, and these were found throughout the parenchyma as far as the ventricular wall itself. In some animals there was an increase in M2 positivity in the SVZ, with many M2-positive profiles densely packed within this area. In addition, many M2-positive profiles within the region between the graft and the SVZ were seen to be oriented towards the lateral ventricle . . . On the side distal to the ventricle, very little M2-positive staining was observed outside the graft core." (*See* Specification, page 35, line 24 through page 36 line 2). Moreover, as demonstrated in Example 15, the transplanted cells continued to proliferate in response to the EGF-infusion. (*See, e.g.*, page 37, lines 1-9).

Thus, Applicant notes that the working examples (in particular Example 15) correlate with the steps recited in the claimed methods, such that the specification is commensurate in scope with the claims. This is all that is required to meet the "how to use" portion of the enablement requirement. Contrary to the Examiner's contention, the instant specification does provide numerous working examples that, taken together, demonstrate how to use the claimed invention.

4. Level of Skill in the Art and Quantity of Experimentation

The Examiner again relies on Jackowski (1995) British J. of Neurosurgery 9:303-17 ("Jackowski") in support of the enablement rejection. According to the Examiner, "Jackowski details the limitations and unpredictability associated with transplantation of neural tissue." (*See*

7/16/02 Office Action, at page 4). Applicant submits that the Examiner's reliance on this article is misplaced.

Jackowski focuses on the difficulties associated with the regeneration of adult mammalian CNS and PNS axons (*i.e.*, differentiated neural cells) (*See* Jackowski, page 311, col. 1, ¶ 2). In contrast, the claimed invention is concerned with *in* vivo regulation of undifferentiated neural stem cells capable of differentiating following transplantation in the brain of living host. Jackowski does not address the transplantation of neural stem cells. Jackowski is nonanalogous art.

Moreover, Jackowski also notes that the lack of success of CNS axons in achieving regeneration may be due to insufficient amounts of trophic growth factors available to the adult central neurons (Jackowski, page 309, col. 2, last sentence of ¶ 1). The methods of the claimed invention overcome this problem by locally delivering a mitogenic growth factor to a specific site following neural stem cell transplantation, thereby inducing proliferation and migration of transplanted neural stem cells, which maintain their ability to differentiate into neurons, astrocytes, and oligodendrocytes. (*See, e.g.*, Specification, page 18, lines 1-6). Thus, contrary to the Examiner's contentions Applicant contends that the instant specification does provide guidance for overcoming problems recognized in the art (*see* Office Action, page 7, ¶ 2).

In addition, it is plain from the evidence already of record, multiple scientific publications confirm that transplantation of neural stem cells can be routinely achieved. Furthermore, such transplantation results in a therapeutic benefit to the host.

The Examiner maintains that the papers previously submitted by the Applicant[1/] do not embrace the claimed invention and/or do not demonstrate the establishment of a therapeutic benefit (*See* Office Action at pp. 6-7). However, Applicant contends that both the specification as well as the evidence of record demonstrate that the ordinarily skilled artisan with this specification in hand could use the claimed invention to transplant undifferentiated neural stem

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1/ *See, e.g.*, Qu et al., Ageing 12:1127-32 (2001); Akiyama et al., Exp. Neurol. 167:27-39 (2001) ("Akiyama"); Kurimoto et al., Neuroscience Letters 306:57-60 (2001); Nishida et al., Investigative Ophthalmology & Visual Science 41:4268-74 (2000); Reubinoff et al., Nature Biotech 19:1134-40 (2001); Mitome et al., Brain 124:2147-61 (2001); Milward et al., J. Neurosci. Res. 50:862-71 (1997) ("Milward"); Zhang et al., Proc. Natl. Acad. Sci. USA 96:4089-94 (1999) ("Zhang"); Brustle et al., Nature Biotechnol. 16:1040-44 (1998) ("Brustle"); Yandava et al., Proc. Natl. Acad. Sci. USA 96:7029-34 (1999) ("Yandava"); Flax et al., Nature Biotechnol., 16:1033-39 (1993); Fricker et al., J. Neurosci. 19:5990-6005 (1999); Aboody et al., Proc. Natl. Acad. Sci. USA 97:12846-51 (2000); Temple et al., Nature 414:112-17 (2001); and Pluchino *et al.*, Nature 422:688-94 (2003) ("Pluchino").

cells *in vivo*, thereby enhancing the effectiveness of the transplanted cells used as a restorative therapy for neurodegenerative diseases.

Likewise, Applicant submits herewith two additional papers, which also demonstrate that the transplantation of neural stem cells results in a therapeutic benefit to the host. Specifically, Ishibashi et al., J. Neurosci. Res. 78:215-23 (2004) (courtesy copy enclosed) demonstrated that, when transplanted into lesioned Mongolian gerbil brains, neural stem cells cultured according to the methods disclosed in the instant application (*see, e.g.*, page 216, 2nd column) "induced significant improvement in the sensorimotor and cognitive functions of the gerbils after focal ischemia." (page 220, 2nd column). Similarly, Ogawa et al., J. Neurosci. Res. 69:925-33 (2002) (courtesy copy enclosed) demonstrated that neural progenitor cells transplanted into a rat spinal cord injury model resulted in both Neurogenesis and functional recovery. (*See, e.g.*, page 928, 1st column; page 929, 1st column).

The Examiner contends that the papers submitted by the Applicant do not show that the precise methods of the claimed invention would provide a therapeutic effect to the host. The methods employed in these papers are shown to provide a therapeutic benefit of the host. One skilled in the art would recognize that these papers demonstrate that the improvement of delivering a mitogenic growth factor according to the claimed methods would also provide a therapeutic benefit to the host.

Moreover, Applicants note that the United States Patent and Trademark Office has already allowed several patents directed neural stem cells suitable for on-demand implantation *in vivo* wherein the cells migrate from the implantation site to another anatomic site for integration within the nervous system of the living host. (*See, e.g.*, United States Patent No. 6,528,306; 6,541,255; and 5,958,767).

Notwithstanding the extensive detail and working examples in the specification and the extensive evidence of record, the Examiner nonetheless contends that the "how to use" prong of the enablement requirement requires demonstration of a therapeutic benefit and that this is not met. The "how to use" requirement of § 112, first paragraph, is satisfied if, as here, "the specification contains within it a connotation of how to use the claimed invention." As demonstrated above, the specification provides far more than the required connotation – it

contains detailed teachings and working examples. Specifically, the methods described in Example 15 parallel those recited in the claimed invention.

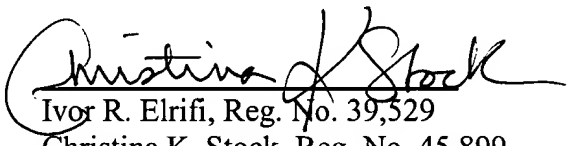
On these facts, and on the basis of the above remarks, Applicant submits that the enablement rejection should be withdrawn.

E. Conclusion:

Applicant submits that this paper is fully responsive and that the application is in condition for allowance. Such action is respectfully requested. Should any questions or issues arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

No additional fees are believed due in connection with this paper. However, the Commissioner is authorized to charge any additional fees that may be due, or to credit any overpayment, to Deposit Account No. 50-0311, Reference 17810-513 (SCI-13).

Respectfully submitted,



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Date: November 30, 2004

TRA 1959821v3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS:	Björklund (as corrected)		
SERIAL NUMBER:	60/160,553	EXAMINER:	N/A
FILING DATE:	October 20, 1999	ART UNIT:	N/A
FOR:	EGF INFUSION STIMULATES THE PROLIFERATION AND MIGRATION OF EMBRYONIC PROGENITOR CELLS TRANSPLANTED IN THE ADULT RAT STRIATUM		

MAIL STOP PETITION
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CORRECTION OF INVENTORSHIP OF PROVISIONAL APPLICATION UNDER 37 C.F.R. §§ 1.48(d) and (e)

Pursuant to 37 C.F.R. § 1.48(d), the undersigned hereby requests the correction of inventorship of the above-identified application. This Request is accompanied by a check (#19674) in the amount of $50.00 for the processing fee set forth in 37 C.F.R. § 1.17(q), and as required by 37 C.F.R. § 1.48 (d)(2).

Specifically, the Applicant wishes to add Anders Björklund as an inventor to this application. The error in failing to name Anders Björklund occurred without deceptive intent on his part.

Based upon the pertinent facts presented herein, the undersigned hereby respectfully requests consideration and grant of this petition for correction of inventorship in a provisional application, pursuant to 37 C.F.R. § 1.48(d).

Moreover, pursuant to 37 C.F.R. § 1.48(e), the undersigned also hereby requests that inventor Rosemary Fricker be removed as an inventor of the above-referenced application. This Request is accompanied by a statement from Rosemary Fricker (now Rosemary Fricker-Gates) that the inventorship error occurred without deceptive intent on her part pursuant to 37 C.F.R. § 1.48(e)(2). Also provided is a check (#19675) in the amount of $50.00 for the processing fee set forth in 37 C.F.R. § 1.17(q). Applicant notes that no assignment was executed by Rosemary Fricker for the above-referenced application. Accordingly, written consent of the assignee pursuant to 37 C.F.R. § 1.48(e)(4) is not believed to be necessary.

Based upon the pertinent facts presented herein, the undersigned hereby respectfully requests consideration and grant of this petition for correction of inventorship in a provisional application, pursuant to 37 C.F.R. § 1.48(e).

Please charge any additional fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No. 17810-513 PRO (SCI-13 PRO). A duplicate copy of this Request is enclosed.

Respectfully submitted,

Dated: November 30, 2004

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